DR. RUBINSTEIN: Yes.

DR. REDMAN: Yes, but it's still a poor instrument.

(Laughter.)

DR. BLAYNEY: Yes.

DR. NERENSTONE: So then, the question is, do the data represent significant evidence of clinical benefit that outweighs the toxicity of treatment?

Sorry. 10 yes, 3 no.

The second part. Do the data represent significant evidence of clinical benefit that outweighs the toxicity of treatment?

Is this really the approval question? Not yet, okay.

DR. TEMPLE: No. But because it includes both evidence of benefit and toxicity, it's very close. Maybe we should have written it differently.

DR. NERENSTONE: Dr. Blayney?

DR. BLAYNEY: Yes.

DR. REDMAN: Abstain.

DR. RUBINSTEIN: No, but I'd like to say that this begs the question of whether the preventive goals have been addressed adequately and whether the FDA's objections to using the preventive data are something that we agree with.

DR. PAZDUR: We can come back to that question.

DR. NERENSTONE: Okay, we'll come back to the preventive as an endpoint.

So, you're a no. Correct?

DR. RUBINSTEIN: I'm a no.

DR. TEMPLE: Stacy, before you leave that, it's worth remembering that even the company's analysis for each study doesn't show a benefit, including the preventive. So, keep that in mind too.

DR. PELUSI: No.

DR. SLEDGE: No.

DR. NERENSTONE: No.

DR. PRZEPIORKA: Abstain.

DR. CARPENTER: No.

DR. LIPPMAN: No, again for the reasons that Dr. Glisson reiterated. We just don't have the data. We don't have the data of the control rates in the placebo. I think that's why I say no.

MR. GRUETT: No.

DR. ALBAIN: Abstain.

DR. KELSEN: No.

DR. GLISSON: No.

DR. NERENSTONE: There are 3 abstentions, 1 yes, and 9 noes.

Question 2. Do the following data on response

rate independently represent clinical benefit of treatment with the CEG that outweighs its toxicity in the treatment symptomatic of recurrent head and neck cancer? Does the response rate represent clinical benefit?

They remind you that 65 percent of the patients that were responding were from stratum 1, or tumors less than 5 centimeters cubed.

Dr. Glisson?

DR. GLISSON: No.

DR. KELSEN: I'm going to interpret this to mean does shrinkage alone mean something clinically, and my answer is no.

DR. ALBAIN: I don't think we know. I'm going to abstain again. I've never abstained in three years. It's two in one vote.

MR. GRUETT: No.

DR. LIPPMAN: No.

DR. CARPENTER: No.

DR. PRZEPIORKA: No.

DR. NERENSTONE: No.

DR. SLEDGE: No.

DR. PELUSI: No.

DR. RUBINSTEIN: I'm going to interpret to this to mean that whatever clinical benefit may or may not pertain to the response rate outweighs the toxicity, and on

that basis, I say yes.

DR. REDMAN: Again, this is the bona fide response rate, not the clinical benefit. This is the clinical tumor shrinkage response rate.

Based on the question, I'd have to say yes.

DR. BLAYNEY: Yes.

DR. NERENSTONE: 1 abstention, 3 yes, 9 noes.

Number 3. Please discuss the clinical value of local treatments for head and neck cancer in patients with systemic disease or patients with locoregional progression.

DR. PAZDUR: You've kind of done this already, for the sake of time.

DR. NERENSTONE: Right. Do you want a vote?

DR. PAZDUR: There's no vote possible. It's a discussion point and I think we've discussed this already.

DR. NERENSTONE: Number 4. Do these trials provide substantial evidence that the cisplatin gel is safe and effective in the treatment of symptomatic recurrent head and neck cancer?

DR. TEMPLE: I think before you do that, you have to do Dr. Albain's question because you can provide substantial evidence for a surrogate approval too and then your standards are different. So, until you grapple with that, at least a little bit, you can't really answer this.

DR. WILLIAMS: One issue that would have to be

addressed before you grapple with accelerated approval would be that the population that was studied had no alternative therapies. That was not the whole population. So, there's some difficulty in discussing that. Do you have any suggestions?

DR. TEMPLE: Well, that's a reminder of what accelerated approval refers to. It means there has to be no alternative or no good alternative or this is better than existing alternatives, and it has to be for a serious or life-threatening disease. I guess that one is fairly easy.

DR. WILLIAMS: I guess what I'm saying is I guess before we really grappled with it as an agency, we'd have to do some more review of the application to see how many patients there were that had no available therapy and what the response rate was. So, whatever you discuss begins with the caveat that we may then decide that there's not sufficient data.

DR. PAZDUR: Here again, the actual ruling on this is that the response rate or the surrogate endpoint must reasonably likely be predictive of clinical benefit. We'd just like to remind people that there has to be this link. It's just not that it's there. The size of the lesions, the location of the lesions might come into play here. What is the magnitude of a local response rate since

we do not have a lot of experience in dealing in this area?

DR. WILLIAMS: I think it sort of goes back to Dr. Carpenter's comment. If you believe that this trial was designed with a reasonable chance of finding clinical benefit and didn't, then I think that's a problem for going forward with those discussions. If you believe that the trial was so insufficiently designed or powered to detect it, so that you believe that it's reasonably likely that the response does predict clinical benefit, I think that would have to be the circumstance under which you made further discussion of the issue.

DR. NERENSTONE: Just one comment about this. I'll open up the discussion. Talking to Dr. Couch who, as I said, is a head and neck surgeon, we talked about, well, what about these big tumors where you're worried. And I think that gets back to Dr. Lippman's concern. We saw the high response rate, but it's really in the small tumors that really are not causing life-threatening problems, at least at the time they're being treated. The whole issue of prevention is another whole issue.

But at least in terms of response rate, her feeling was that this drug is extraordinarily unsafe for large tumors in the neck especially because of the prior surgeries. Her feeling was that was exactly the patient population who you want to treat because you have very

little options, but in whom the toxicity is much too high, and that the worst thing you want to do with these patients is hasten their demise by a product that has questionable benefit.

DR. LIPPMAN: I don't know how often this happens, but I assume there are some cases where you do reflect and we reflect to the sponsor that there's some very provocative findings here that we'd like to see followed on and evaluated along the lines we've indicated. To me that isn't synonymous with accelerated approval.

DR. WILLIAMS: Right. I agree.

DR. TEMPLE: Accelerated approval means it gets marketed while that happens, and a good suggestion means it doesn't.

DR. LIPPMAN: Right. That's where, as I indicated before, I draw the line. I'd like to see some of this followed up, but I don't think we have the data now to make an accelerated approval.

DR. WILLIAMS: Why don't I go ahead and suggest a question? Based on these data, do you think this tumor response rate is reasonably likely to predict clinical benefit after all that we've been through here? That's the first question that I think is reasonable to ask.

DR. NERENSTONE: Do you want a vote?

DR. PAZDUR: That's the essence of the

accelerated approval. So, basically would the response rate presented in small tumors -- in fact, many of these occurred in stratum 1 or the majority occurred in stratum 1. Would this be reasonably likely to predict for clinical benefit?

DR. NERENSTONE: Grant, do you want to repeat the exact wording so that Karen can get it down?

DR. WILLIAMS: Okay. Would the response rate which has been seen in these trials be reasonably likely to predict clinical benefit? I mean, it's in these trials. These are the trials that we have. So, we don't need to specify. It's what these trials were.

DR. FRYKMAN: I'd like to add one comment, and that has to do again with accelerated approval. The presumption with accelerated approval is that there is an association between the surrogate and the actual clinical benefit. Again, we'll go back to the data that was presented here. Even under the sponsor's analysis, let alone the FDA's analysis, that linkage or what we're calling a linkage is actually very weak. In our more conservative analysis, it was 13 percent in the 414 study and 38 percent in the European study, which was conducted better. So, it seems to me that there is good evidence that there is no association.

DR. NERENSTONE: Dr. Temple.

DR. TEMPLE: If you believe the numbers, a 40 or 50 percent sensitivity, I don't believe it's reasonable to call that very weak. That would be very impressive if it were true. What you've heard is discussion of why our review doesn't think that it's true. So, I don't think that's the problem.

I think the problem is what you're talking about. Is the observed response rate, given the clinical data -- you're allowed to look at that -- something that makes you think that these responses are likely to lead to clinical benefit, with all the reservations people have said, that they're small, that to the extent people have been able to look at this endpoint, you didn't see that much, but you didn't see absolutely nothing. All of those things. How does that add up?

And then later on, you'd weigh that against the observed toxicity, but that's a different question.

DR. WILLIAMS: I think basically the credibility of the data from this instrument -- if we believe that the data are credible -- we believe that there was no result. If you don't believe the data are credible, then I think there could have been a result there that we didn't see. And it would fall back to your original suspicion or reasonable likeliness that there is a correlation.

DR. NERENSTONE: So, do you want us to vote on this? Okay.

DR. RUBINSTEIN: Could I just make one statement? The response rate for stratum 2 is 21 percent. Now, that may be considered low, but it's there. The response rate for stratum 1 is 37 percent. So, there definitely is a difference, but it's not that all the responses are occurring in stratum 1.

DR. SRIDHARA: Overall, of the responses that are there, two-thirds of them are coming from stratum 1, and one-third are coming from stratum 2.

DR. NERENSTONE: The question before us, will the response rate presented in these trials be reasonably likely to predict clinical benefit? Dr. Glisson, why don't we start with you.

DR. GLISSON: Yes. I believe we actually already voted on this issue. I'll say no again.

DR. KELSEN: No.

DR. ALBAIN: Possibly.

(Laughter.)

DR. NERENSTONE: You only have three choices: yes, no, or abstain.

DR. ALBAIN: All right. I will do it again. Yes.

MR. GRUETT: No.

DR. LIPPMAN: Again, this is related to question 2, which I think is what Dr. Glisson was referring to. I had my hand up because it would be nice to qualify the question a little bit just to indicate response rate and response duration because that's really what I'm looking at. There was an overwhelming percentage of CRs here and they were very durable. So, the response rate itself for the CR rate -- I don't know how I'd interpret that, but the fact that the median durations were 2 to 3 months influences my answer of no.

DR. WILLIAMS: It's meant to reflect the CR, PR, and duration.

DR. LIPPMAN: So, your question reflects duration also.

DR. WILLIAMS: Right.

DR. LIPPMAN: No.

DR. CARPENTER: Yes.

DR. PRZEPIORKA: Not to upstage Scott, but as Dr. Rubinstein pointed out, the CR rate is pretty impressive. If you actually go through the breakdown of who responds the most, it's people with oropharyngeal lesions which may be less than 5 centimeters, but they're in a very small space unless they're a Steelers' fan or something.

Time to progression, as he pointed out, is

better with the gel.

There is a higher dropout rate in the placebo because of greater progression in the placebo. So, people on the treatment arm aren't dropping out because of toxicity, and in fact, if you look at dropouts for toxicity, they aren't very much different.

I think the tool that they used to look for clinical benefit is absolutely crummy. There are all sorts of other indicators that there's probably clinical benefit there, but somebody has to figure out what it is.

So, the answer to the question is yes.

DR. NERENSTONE: No.

DR. SLEDGE: No.

DR. PELUSI: No.

DR. RUBINSTEIN: Yes.

DR. REDMAN: Yes.

DR. BLAYNEY: My answer is yes. I think that this is going to get applied early in the clinical course before tumors get huge, and they can probably pick some critical areas to get at the clinical benefit.

DR. NERENSTONE: And the results are 6 yes, 7 noes. Pretty evenly divided there.

Do we hit number 4?

DR. TEMPLE: But you do have to divide the last into conventional and --

DR. PAZDUR: Well, that's the next question. The last question is basically safe and effective and demonstrating clinical benefit.

DR. TEMPLE: We'll take the previous vote as meaning the people who thought yes would probably agree that it should be approved under accelerated approval. And this is the question about not under accelerated approval.

DR. NERENSTONE: So, number 4 is for standard approval.

DR. PAZDUR: Yes, demonstration of clinical benefit.

DR. NERENSTONE: Do these trials provide substantial evidence that the cisplatin gel is safe and effective in the treatment of symptomatic recurrent head and neck cancer? So, the application as it stands now for regular approval.

Dr. Blayney?

DR. BLAYNEY: No.

DR. REDMAN: This is for regular approval.

DR. NERENSTONE: This is for the application we have now.

DR. REDMAN: No.

DR. RUBINSTEIN: No.

DR. PELUSI: No.

DR. SLEDGE: No.

DR. NERENSTONE: No.

DR. PRZEPIORKA: No.

DR. CARPENTER: No.

DR. LIPPMAN: My answer is no, but I again think I'm not sure the vote would have been the same if it was listed as accelerated approval. I don't know how important that is to you, but I think --

DR. TEMPLE: We're assuming that. We're assuming the previous vote represents accelerated approval. 7 noes, 6 yes.

DR. LIPPMAN: I'm not sure that's the case. I'd be interested to see what the vote is if accelerated approval is put on the table. So, if that's important to you, it might be worth voting on it.

But the answer to this question is no.

MR. GRUETT: No.

DR. ALBAIN: No.

DR. KELSEN: No.

DR. GLISSON: No.

DR. NERENSTONE: Do you want an accelerated approval vote?

DR. PAZDUR: If would like to. We considered the previous question reasonably likely to demonstrate clinical benefit equivalent to an accelerated approval because that is the criteria that we would use to make that

decision.

DR. NERENSTONE: Do you want it to be explicit, committee, so that you understand that's what we're now talking about? So, if this application were an accelerated approval, meaning that there would be phase IV commitments to do other studies to show clinical benefit, because that's the only way it could get full approval is if clinical benefit were shown under the rules of accelerated approval, so that we would approve this application with those further commitments.

DR. PAZDUR: And the drug would be fully marketed here also, commercially available.

DR. WILLIAMS: As opposed to the previous question, your vote would indicate that you do think that the response rate is reasonably likely to predict clinical benefit, and for that reason, it's reasonable for us to approve the drug and then demonstrate the clinical benefit. So, by voting for accelerated approval, you'd also be voting the previous question.

DR. TEMPLE: It implies that the benefit suggested by the response rate outweighs whatever risks there are too. So, that is a little different from the previous question.

DR. LIPPMAN: And the drug would be marketed and then used.

DR. PAZDUR: Correct.

DR. NERENSTONE: But there would have to be a commitment for a phase IV trial. Is that likely to get done?

DR. PAZDUR: That's what you have to consider also in making a determination here because the negotiation with the company is that these trials would be done with due diligence.

DR. NERENSTONE: Okay. To restate the question, should this be approved under the accelerated approval mechanism? Dr. Blayney, would you like to start?

DR. BLAYNEY: I'm going to --

DR. HOWELL: Madam Chairman, a point of information. The company has indicated that it is more than happy to make that phase IV commitment.

(Laughter.)

DR. NERENSTONE: A wise business decision.

(Laughter.)

DR. PAZDUR: They haven't heard what the phase IV commitment is, though.

(Laughter.)

DR. NERENSTONE: We'll have some discussion. I think this is going to be a very important vote. Dr. Albain.

DR. ALBAIN: I think it would be absolutely

critical that a panel of head and neck surgeons, ENT oncologists, medical oncologists that major in head and neck cancer be involved in a detailed prescription for the labeling that goes beyond just the fine print, but a box portion that would address all of Dr. Couch's concerns and many of the rest of us about in which patients this should be applied once it's on the market.

DR. NERENSTONE: Dr. Sledge.

DR. SLEDGE: I think we need a little reality testing here. This trial took six years to accrue. I've heard several people around the table, including several of those who think this is a wonderful idea for accelerated approval, say that the instruments used in this trial were crummy. I heard that word from more than one person. So, what we're talking about is developing a new instrument, validating it, and then doing a larger phase III trial? I mean, whose grandchildren are going to approve this drug?

(Laughter.)

DR. NERENSTONE: Dr. Rubinstein.

DR. RUBINSTEIN: Yes, those concerns aside --

(Laughter.)

DR. RUBINSTEIN: What is the usual procedure? Is a window set of some number of years?

DR. PAZDUR: Well, we follow these commitments, but the actual wording is -- and it is one for the

interpretation of the division and the agency -- with due diligence basically. We need to have a realistic expectation that this trial can be done vis-a-vis Dr. Sledge's comments.

DR. NERENSTONE: In most cases, though, as a point of information, we don't usually do it this way. That is, an application comes where there is a response rate, and it's in a situation where there are no other options available. Then because you want the drug on the market, you say, we think that this response rate is going to translate into clinical benefit as we define it in the future for a phase IV commitment. So, this is a little bit different interpretation in the process of drug development.

DR. PAZDUR: Here again, there are some caveats here. We would have to take a look at the number of patients that truly represent an unmet medical need here.

Please remember also that this would be precedent setting in the sense that other people that fail their clinical trials could make claims that they have underpowered trials, that they used inappropriate scales to measure clinical benefit, et cetera, and they could come back and say, well, can we now have accelerated approval. So, this is somewhat a precedent-setting situation.

I don't know, Bob, if this has happened before.

DR. TEMPLE: Undoubtedly.

What's unusual about it is that usually you have a trial that was only looking at response rate. So, you didn't not find a clinical benefit. There was never any chance that you were going to find a clinical benefit. Here there was an attempt to look at a clinical benefit.

But people have said two opposite things. Some have said it was a good shot, used a good endpoint. Well, it was a little too small but it wasn't that small. So, that in some sense, if you believe that, argues that they've already tested that question.

If, in contrast, you believe that the endpoint was crummy and the size of the study gave them almost no hope, then you might believe that, even though they tried, the clinical endpoint has not been assessed and that there is a reasonable possibility that sometime in the next 30 years they would succeed in doing it.

So, it is a little unusual that way.

DR. NERENSTONE: I do want to remind the committee that we had a similar problem with oxaliplatin, if you remember. The endpoints that were in the application were not fulfilled, and there we encouraged the investigators to reapply with a better endpoint. We did not go for accelerated approval. So, that's just to remind people we have been in this situation before where we think

there is a drug with a response rate that might be significant.

Dr. Pelusi.

DR. PELUSI: I guess one of the things that bothers me is that I think we're all struggling with the fact that you see some response, and we all want that to be a good response. But when we look at the numbers in the community, and you're asking physicians to do a procedure that they may not do a lot of, the question is, where is it the safest done?

So, if we really start to look at that, I think that that puts something else on the table in terms of is there a subset of patients that maybe should be treated at a certain setting where people actually have that type of experience versus trying to do one every one or two years and not have the skills that some of the people --

DR. PAZDUR: Part of accelerated approval could allow us to restrict access to this drug and have it be used at only specialized centers if that is what you are suggesting.

DR. PELUSI: Well, I guess I'm struggling with that because if it just goes on the market, the question is then is it a free-for-all, and I don't think any of us would intend that to be so.

DR. NERENSTONE: Mr. Gruett.

MR. GRUETT: In an accelerated approval, aren't you offering the patients hope? And I don't believe there's enough hope generated here to offer that feeling within the patients. I would more look at going back into a phase III trial then going into an accelerated approval trial.

DR. NERENSTONE: Dr. Przepiorka.

DR. PRZEPIORKA: Two comments. I think if there is a phase IV commitment to do a clinical benefit analysis in another trial, there better be some urgency in getting the tool done and validated, and if it is done successfully, it will make a major contribution to oncology because there are other situations in which such a tool would be valuable.

With regard to the caveat that Rick brought up, I would hope that in the future, if clinical benefit is going to be a primary outcome, that the FDA has to slam the door and put clinical trials on hold rather than just give some advice and hope that the companies will follow it and that it is not going to let the company go ahead and do a trial where the statistical section is not completed and then turn around and --

DR. PAZDUR: Donna, things have changed since then. Obviously, there are special protocol assessments which we've implemented basically for all of our protocols

going through that lock us into agreements, and those protocols are reviewed. The provisions for special protocol assessment have occurred after these protocols were initiated. So, unfortunately, there's a lag time here that the party was not able to benefit from that.

DR. NERENSTONE: Dr. Howell.

DR. HOWELL: Just a point of clarification for the committee. A subsequent trial combining IntraDose with systemic chemotherapy is well underway with a variety of other clinical benefit endpoints.

As you all noted, there are a lot of problems with this instrument. That doesn't mean that an appropriate instrument cannot be found and cannot be used to make a good association between tumor response rate, which we all agree is there, and clinical benefit. I think we would ask for your consideration in giving the sponsor the opportunity to try to nail down exactly this kind of issue for the purpose of broadly helping the whole field.

DR. NERENSTONE: But that can be done without granting accelerated approval. That study is ongoing.

DR. HOWELL: I remind you that this is a tiny patient population who have no other therapeutic options. I would doubt very seriously that this randomized trial would ever be done if there isn't encouragement from a regulatory strategy moving forward in this disease.

DR. NERENSTONE: Dr. Frykman.

DR. FRYKMAN: Yes. I just wanted to make one comment from the FDA perspective. If accelerated approval is considered and in fact it's granted, then we still have to write a label for this drug. As you recall, in the trial there were a number of dosing errors. In fact, frankly, the truth of the matter is we don't know what dose to have in the label. The sponsor proposes .25 ml per cc, and there's some evidence that was in the briefing document that that may, in fact, not be the right dose. It might actually provide an inferior response rate compared to the .5 ml per cc of tumor.

So, I would like to see if it's possible for the phase IV commitment, if that is even being considered, that in fact a consideration of reformulation and perhaps increasing the concentration, while keeping the volume of the gel down while still providing the same amount of platinum per tumor, might be a useful way to go.

DR. HOWELL: A point of information: That cannot be done, sir. You're at maximum concentration of drug in this gel.

DR. NERENSTONE: Last comment, because otherwise we're going to be here till midnight. Dr. Lippman.

DR. LIPPMAN: The issue of sending

encouragement to the sponsor to follow that -- I mean, I think there must be other ways other than accelerated approval to do that. We've had this discussion. People are intrigued. There's definitely clinical activity here in terms of tumor responses. I think we've suggested some ways to address that and that we do think -- at least the sentiment of the committee -- a number of us do think it should be followed up. And that's not the kind of encouragement we give every application, as you know. It hardly ever comes up.

DR. PAZDUR: You should vote for this because it is reasonably likely to predict clinical benefit, not on the basis of sending messages to sponsors.

DR. TEMPLE: Because you believe it is. He's not telling you what to vote.

DR. NERENSTONE: Let's take a vote and everybody can have their last comment as we go around. The question is, should this be approved under the accelerated approval mechanism? Dr. Glisson.

DR. GLISSON: No.

DR. KELSEN: No.

DR. ALBAIN: Yes.

MR. GRUETT: No, but I'd like to see more phase III study.

DR. LIPPMAN: No. Ditto to that last comment.

DR. CARPENTER: Let me think a minute.

DR. PRZEPIORKA: Yes.

DR. NERENSTONE: No.

DR. SLEDGE: No.

DR. PELUSI: No.

DR. RUBINSTEIN: Abstain because I'm concerned that if we did go for accelerated approval, we would actually make the trial harder to do if the drug were commercially available.

DR. REDMAN: I think clinically something is going on, but I can't agree to letting the drug out on the market.

DR. NERENSTONE: I take it that's a no.

DR. REDMAN: No.

DR. BLAYNEY: I'm going to vote yes to be consistent with my previous votes, although I'm wary of setting a precedent here.

DR. NERENSTONE: Dr. Carpenter.

DR. CARPENTER: No.

DR. NERENSTONE: 1 abstention; yes, 3; 9 noes.

Thank you very much for this marathon session. We will begin tomorrow at 8 o'clock.

(Whereupon, at 7:03 p.m., the committee was recessed, to reconvene at 8:00 a.m., Tuesday, September 11, 2001.)